Clinical Trial/Experimental Study

Medicine

OPEN

Treatment of anal fistula using a decellularized porcine small intestinal submucosa plug

A non-inferiority trial

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Abstract

Background: Using small intestinal submucosa (SIS) has increasingly become the standard method for the treatment of anal fistula. The porcine SIS manufactured by Biosis Healing is a novel biological material that has several advantages for the safe and effective repair of tissues. Our study aimed to verify the efficacy and safety of the decellularized porcine SIS (VIDASIS) anal fistula plug.

Methods: We conducted a non-inferiority multicenter, randomized, controlled clinical trial involving patients with chronic anal fistula. Patients from 3 centers across China were randomized 1:1 to Biosis SIS vs commercial SIS. The primary endpoint was the healing rate and secondary endpoints included recurrence within 6 months, rate of copracrasia, healing time, pain using a visual analog scale, and patient and doctor satisfaction.

Results: A total of 186 patients were randomized. Of these, 82 patients in the Biosis SIS and 81 in the control (commercial) SIS completed the trial (per-protocol set). The healing rate at the 6-month follow-up (full analysis set) was 92.0% for the Biosis SIS and 89.8% for the control SIS (P = .620). The rate difference of 2.2% (full analysis set; 95% confidence interval: -6.4% and 10.7%, respectively) was within the pre-specified non-inferiority margin of -10%. There were no differences between the 2 groups with regard to the secondary endpoints. No serious adverse event or death occurred.

Conclusion: Our study shows that the VIDASIS anal fistula plug manufactured by the company Biosis Healing is safe and effective and is not inferior to existing commercial SIS materials.

Abbreviations: FAS = full analysis set, SAS = statistical analysis system, SIS = small intestinal submucosa, VIDASIS = decellularized porcine small intestinal submucosa.

Keywords: anal fistula, randomized controlled trial, small intestinal submucosa, VIDASIS

1. Introduction

Anal fistula (or anorectal fistula) is an abnormal tract or cavity of granulation tissue connecting the anal canal or rectum to the perianal skin.[1,2] It is a common illness and mainly occurs after the rupture or incision of an anorectal abscess.[3,4] The shrinking of the abscess accompanied by continuous entering of intestinal contents into the abscess cavity could lead to circuitous abscess canal, which results in insufficient drainage and is very difficult to heal.[3,4] Anal fistula commonly occurs especially in young adults. The prevalence of anal fistula is higher in men than in women.[1,2,4] It accounts for 3.6% of the overall incidence of all anorectal diseases in China, with the highest prevalence in men aged 20 to 40 years.[5]

Anal fistula mainly consists of the primary internal outlet, fistula canal, and secondary external outlet. In general, there is only 1 internal outlet, which is located near the dentate line. However, several external outlets may be present around the anus. Currently, surgery is the most effective treatment method for anal fistula.[1–4] Surgical procedures mainly include syringotomy and fistulotomy (assisted with or without thread-drawing therapy). Other procedures such as fistula exclusion, transanal rectal advancement flap repair, thread-drawing therapy, and staged syringotomy have been attempted; however, the high

The study was supported by Capital Health Research and Development of Special (2018-1-2032).

The authors have no competing interests to declare.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study protocol was approved by the Ethics Committee of the institution responsible for the trial before the study was conducted. All patients provided signed informed consent prior to the study procedure. The trial registration number is ChiCTR1900023829.

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How to cite this article: Chen ZW, Zheng Y, Zhao R, Wang ZJ. Treatment of anal fistula using a decellularized porcine small intestinal submucosa plug: A non-inferiority trial. Medicine. 2022;101:29(e29110).

Received: 1 May 2021 / Received in final form: 1 March 2022 / Accepted: 1 March 2022

http://dx.doi.org/10.1097/MD.0000000000029110

rates of recurrence, sequelae, and complications have posed as challenges. Moreover, evidence to recommend any single procedure over the others is insufficient.[6] In recent years, attention has been paid to protecting the anal functions of patients with anal fistula. Minimally invasive surgery has been advocated to minimize the damage to anal functions, especially to the anal sphincters.

Small intestinal submucosa (SIS) is a processed extracellular matrix that is capable of retaining the properties of the native tissue. Porcine SIS is a bioprosthetic collagen material, and has a natural extracellular matrix with high affinity to human tissues. These properties make SIS is an ideal material for the repair of soft tissues, with good histocompatibility and low immunogenicity.[7–9] Anal fistula treatment using decellularized porcine SIS (VIDASIS) is minimally invasive method, and the procedure is simple to perform.[10,11] The treatment involves less postoperative pain and no rejection or toxic side effects, and the success rate is relatively higher than existing treatment options; therefore, it is considered as a major breakthrough in the treatment of anal fistula.

The Biosis Healing Biological Technology Co., Ltd. (Beijing, China) has successfully developed an anal fistula plug composed of regenerative extracellular matrix material derived from VIDASIS. Compared to the commercial SIS from Cook Medical (Biodesign, Bloomington, IN), SIS from Biosis has lower residual DNA and α-gal, higher safety, and lower immunogenicity.[12] In addition, the hydration time of the 2 anal plugs is different: 5 to 10 minutes for the Biosis SIS, not exceeding 2 minutes for the Cook Medical SIS. Animal studies have shown the advantages of the Biosis SIS in different medical applications,[12] but data from actual implantation in humans is scarce. Therefore, the aim of the present clinical trial was to verify the efficacy and safety of the anal fistula treatment using the SIS anal fistula plug from Biosis Healing.

2. Materials and Methods

2.1. Study design and patients

Our study was a non-inferiority multicenter, randomized, controlled clinical trial. Patients with chronic anal fistula (external orifice ≤2) were enrolled from March 30, 2016, to September 12, 2017, at 3 centers across China (Beijing Chaoyang Hospital Affiliated to Capital Medical University, Tianjin People's Hospital, and Peking University Third Hospital). The eligible patients were randomized 1:1 to be treated with the SIS anal fistula plug manufactured by Biosis Healing (experimental group) and a commercial SIS (control group). This trial strictly followed the guidelines of the Declaration of Helsinki and was conducted according to the regulations and standards for the clinical trials in China. The study protocol was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University, Clinical Trial Ethics Committee of Tianjin People's Hospital and Medical Science Research Ethics Committee, Peking University Third Hospital responsible for the trial. All patients provided signed informed consent. The trial registration number is ChiCTR1900023829.

The inclusion criteria were as follows: (1) history of chronic simple low anal fistula for >3 months; (2) 1 fistula; (3) the inner orifice located at the anal sinus; (4) external orifices ≤2[1–4]; (5) patients aged 18 to 75 years; (6) adherence to the doctors' instructions and undergoing re-examinations regularly; and (7) volunteering to participate in the trial and providing signed informed consent.

The exclusion criteria included (1) malignancy; (2) intestinal tumors, intestinal tuberculosis, or Crohn's disease; (3) infectious surgery or severely contaminated operations; (4) severe cardiopulmonary disorders; (5) chronic renal diseases and renal insufficiency; (6) liver diseases and hepatic insufficiency; (7) idiopathic allergic constitution, in particular, allergy to collagen or porcine-derived materials; (8) history of allergy to multiple drugs, with recent allergic reactions; (9) pregnant or lactating women or those planning a pregnancy; (10) participation in other clinical trials within the past 3 months; (11) psychiatric disorders; or (12) patients deemed unsuitable for the trial by the investigators; (13) patients receiving any treatment that could interfere with the results of this study.

The criterion for withdrawal was failure to identify the internal orifice during surgery.

2.2. Randomization

The patients were randomized using a central internet-based system managed by an independent statistician using the central stratified block randomization method. The patient sequence was generated by a special statistical analysis system (SAS) macro program.

2.3. Ligation of the intersphincteric fistula tract (LIFT)-plug procedure

All surgeries at the 3 centers were performed by a chief or deputy chief surgeon with >20 years of surgical experience. Routine cleansing enema was performed before the procedure. The patients received local anesthesia, regional block anesthesia, or general anesthesia, as per their or the surgeons' preference. The skin was disinfected with iodophor. A detector wire was then inserted from the external orifice to locate the internal outlet. This procedure was conducted gently and no additional force was applied when passing through the internal outlet to avoid creating a false internal outlet. The insertion was stopped when the wire was close to the rectal mucosa. A 1.5 to 2.0-cm arch-shaped incision was created along the anal margin at the intersphincteric groove above the fistula canal, under the guidance of the guidewire. The fistula canal was separated along the planes of the internal and external anal sphincters and resected after entering the internal sphincter plane. The internal outlet of the fistula canal at the internal sphincter was closed by suturing with an absorbable thread. The fistula canal was then separated toward the external sphincter and resected. A curette was used to scrape off the infectious granulation tissue in the fistula canal in between the internal and external sphincters. Normal saline with metronidazole was used to rinse the fistula canal, and the fistula canal was confirmed again. Next, the anal fistula plug that was completely hydrated was used to fill the fistula canal. For the experimental group, the plug from Biosis Healing (Beijing Biosis Healing Biological Technology Co., Ltd, Beijing, China) was used, while the plug from Cook Medical (Bloomington, IN) was used for the control group. The internal side of the fistula canal was fixed by suturing with an absorbable thread. The anal fistula plug at the external outlet was trimmed level with the skin. Interrupted basting suturing was performed for the incision between the internal and external sphincters. Sterile dressing was applied at the site where the anal fistula plug was placed.

2.4. Postoperative management

Since the surgery could not be performed under completely aseptic conditions, antibacterial agents were frequently used to prevent infectious complications. Cefoxitin or cefminox sodium (2 g) or ciprofloxacin lactate sodium chloride (0.2 g) was administered b.i.d intravenously. To ensure effective fusion of the tissue and anal fistula plug, the patients were asked to restrict their activities for 2 weeks after surgery. They were not allowed to carry items weighing >5 kg. The patients were instructed to avoid intense activities, and most their activity was restricted

to walking. Sexual activity and use of items like tampons were prohibited. Bathing in a tub was prohibited and only taking a standing shower was allowed. Water could be used to clean the surgical area and relieve irritation.

2.5. Follow-up

The follow-up deadline for this study was February 28, 2018. Outpatient follow-up was performed 1 day, 1 week, 1 month, 3 months, and 6 months after surgery. The patients' vital signs were assessed. Palpation was performed to observe healing and pain. Routine blood and urine tests as well as blood biochemistry tests, including total bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatinine were performed 1 week after surgery.

2.6. Endpoints

The primary endpoint was healing rate, which was classified as follows: (1) healed: complete healing and purulence, pain, fall-swell feeling, and pruritus disappeared; (2) effective: the wound healed and purulence disappeared but pain, fall-swelling feeling, and pruritus evidently improved; (3) response: the wound did not heal and purulence almost disappeared, while pain, fall-swelling feeling, and pruritus improved; and (4) no response: the wound did not heal and the improvements in purulence, pain, fall-swell feeling, and pruritus were not evident. The healing rate was calculated as (number of healed + number of effective)/total number × 100%.

The secondary endpoints included the recurrence rate within 6 months (±15 days) post-surgery, the rate of copracrasia (the objective symptoms of the anus were categorized as grade I, anal functions were normal; grade II: normal defecation control, but the underpants were slightly contaminated by feces or excrement; grade III: control over solid or semi-solid feces but no control over liquid feces; and grade IV: no defecation control), healing time, pain using a visual analog scale (0: no pain, 1 to 3: mild pain, 4 to 6: moderate pain, and 7 to 10: severe pain), doctors' satisfaction rate (according to the convenience of using the product; efficacy of improving wound healing; and occurrence of postoperative adverse events: satisfactory, normal, and unsatisfactory), patients' satisfaction rate (according to the efficacy of the product and the pain while using the plug: satisfactory, normal, and unsatisfactory).

2.7. Safety evaluation

Complications and adverse events such as fever (post-operative day 1), local infection, allergic reaction to the plug, abscess, inflammation, etc, were recorded at the follow-up time points.

2.8. Statistical analysis

The sample size was based on the inferiority principle.[13] Randomization was 1:1, α was 0.025 (1-sided), and power (1-β) was 80%. As the primary efficacy endpoint, the average healing rate was expected to be 95% and the non-inferiority threshold was -10%. As per these percentages, 74 patients were required in each group. Furthermore, considering the follow-up period of 180 days and a drop-out rate of 20%, each group should have consisted of 92 patients, out of a total of 184.

The full analysis set (FAS) refers to all randomized patients who received the anal fistula plug. The per-protocol set included patients who met the eligibility criteria and completed all pre-defined treatments and visits. The safety set included patients who received the anal plug.

The SAS version 9.4 software (SAS Institute, Cary, NY) was used for statistical analysis. A 2-sided statistical analysis was conducted in this study. A P values of <.05 was considered to be statistically significant (except described otherwise). For the description of continuous data, means, standard deviations, medians, minimum value, maximum value, lower quartile, and upper quartile were calculated. Frequencies and percentages were used to describe categorical data. The independent t test or Wilcoxon rank-sum test was used for the comparisons of continuous data between the 2 groups, based on the results of the Kolmogorov–Smirnov test. A chi-square test or Fisher's exact test was used for the comparisons of the categorical data. The Wilcoxon rank-sum test or Cochran–Mantel–Haenszel test was used for the comparisons of the ranked data.

For the primary efficacy endpoint (healing rate), the null hypothesis was that the difference in the healing rate of the 2 groups was lower than or equal to the predefined non-inferiority margin. The alternative hypothesis was that the difference in the healing rate of the 2 groups was higher than the predefined non-inferiority margin.

For the management of missing and abnormal data, the poorest imputation method was used. No imputation was conducted for the other missing data.

3. Results

3.1. Characteristics of the patients

Figure 1 summarizes the enrollment process. Of 200 eligible patients, 10 who did not meet the inclusion criteria were excluded and 4 refused to participate in the trial. Finally, a total of 186 patients were enrolled and randomized: 82 in the Biosis SIS group and 81 in the control group. Table 1 shows the baseline characteristics of the patients. There were no significant differences between the 2 groups, except for history of allergies, which was low in the experimental group (1.2% vs 12.5%, P = .003).

3.2. Primary endpoint (healing rate)

There was no significant difference in the healing rate during the 6-month follow-up period (Table 2). The healing rate during the final follow-up (FAS) was 92.0% for the Biosis SIS group and 89.8% for the control SIS group (P = .620). The difference in the healing rate between the 2 groups was 2.2% (FAS, 95% confidence interval: -6.4% and 10.7%, respectively), which is within the pre-specified non-inferiority margin of -10%.

3.3. Secondary endpoints

The secondary endpoints are listed in Table 3. The cumulative recurrence rate at 6 months was 2.4% in each group (P > .99). No patient showed copracrasia during the study period. Healing time was 34.5 days (29–48 days) in the Biosis SIS group and 36 days (29–73 days) in the control group (P = .795). There were no differences in pain between the 2 groups during the study period (all time points, P > .05). No grade IV pain was observed, and only 1 patient had transient grade III pain. Doctors' satisfaction rate at 6 months was 91.5% in the Biosis SIS group and 92.7% in the control group (P > .99). Patient satisfaction rate was 91.5% in both groups (P > .99).

3.4. Safety

No serious adverse event or death occurred in either group. No patient developed postoperative fever. The local infection rates at 7 days, 30 days, 3 months, and 6 months were 0%, 12.6%, 12.6%, and 10.3%, respectively, in the Biosis SIS group and 0%, 9.1%, 8.0%, and 5.7%, respectively, in the control group (all P > .05). No patient developed allergic reactions to the plug (Table 4).

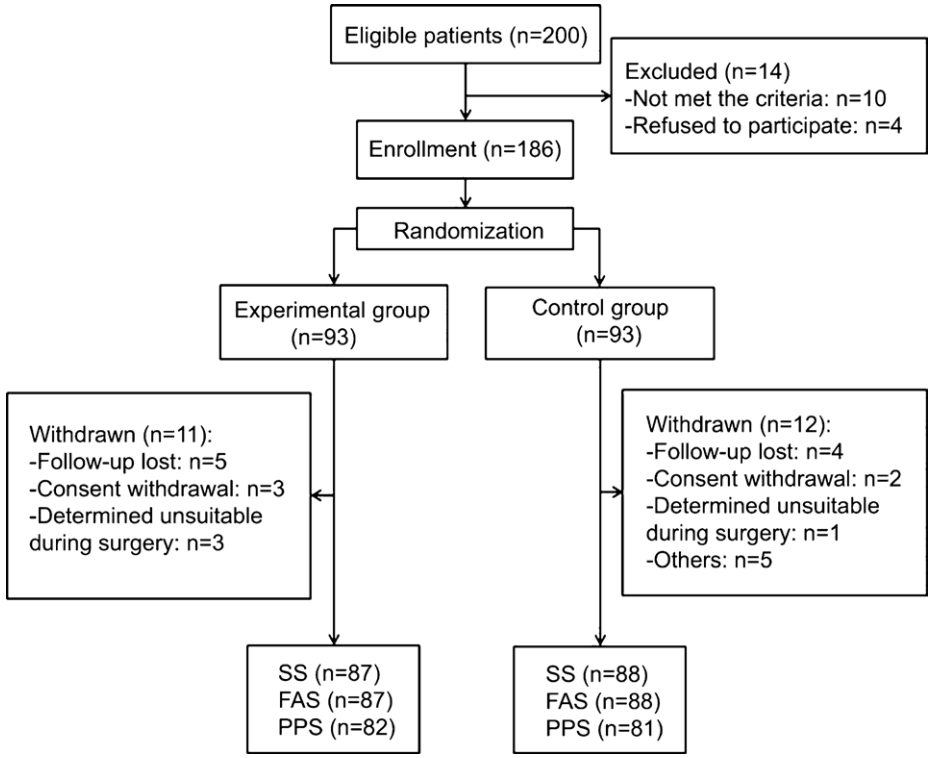

Figure 1. Patient enrollment flowchart.

Table 1

Characteristics of the patients (FAS).

	Experimental, n = 87	Control, n = 88	*P*
Age (yr)	34.0 (27.6–45.7)	32.8 (28.1–42.5)	.478
Male, n (%)	75 (86.2)	78 (88.6)	.628
Height (cm)	172 (169–176)	175 (168.5–178.5)	.079
Weight (kg)	75.9 ± 13.7	76.9 ± 1.7	.648
Allergic history, n (%)	1 (1.2)	11 (12.5)	.003
Systolic blood pressure (mmHg)	124 (119–134)	124 (117–134)	.758
Diastolic blood pressure (mmHg)	80 (72–85)	76.5 (70–82.5)	.150
Heart rate (bpm)	76 (72–80)	76 (70–80)	.996
Respiration rate (bpm)	18 (16–19)	17 (16–19)	.104
External orifices, n (%)			.927
0	9 (10.3)	10 (11.4)	
1	67 (77.0)	73 (83.0)	
2	11 (12.6)	5 (5.6)	

FAS = full analysis set.

Table 2

Primary endpoint [healing rate, n (%)].

	FAS			PPS		
Time point	**Experimental group, n = 87**	**Control group, n = 88**	**P**	**Experimental group, n = 82**	**Control group, n = 81**	**P**
7 d	0 (0)	0 (0)	–	0 (0)	0 (0)	–
30 d	50 (57.5)	46 (52.3)	.471	45 (54.9)	45 (56.3)	.645
3 mo	72 (82.8)	73 (83.0)	.963	68 (90.7)	68 (90.7)	.934
6 mo	80 (92.0)	79 (89.8)	.620	80 (97.6)	78 (96.3)	.676

FAS = full analysis set, PPS = per-protocol set.

Table 3

Secondary endpoints.

Endpoint	Time point or grade	FAS			PPS		
		Experimental group, n = 87	Control group, n = 88	*P*	Experimental group, n = 82	Control group, n = 81	*P*
Recurrence rate, n (%)	7 d	0 (0)	0 (0)	–	0 (0)	0 (0)	–
	30 d	0 (0)	0 (0)	–	0 (0)	0 (0)	–
	3 mo	1 (1.3)	0 (0)	.497	1 (1.3)	0 (0)	>.99
	6 mo	2 (2.4)	2 (2.4)	>.99	2 (2.4)	2 (2.5)	>.99
Copracrasia rate, n (%)	7 d	0 (0)	0 (0)	–	0 (0)	0 (0)	–
	30 d	0 (0)	0 (0)	–	0 (0)	0 (0)	–
	3 mo	0 (0)	0 (0)	–	0 (0)	0 (0)	–
	6 mo	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Healing time, days (only in healed patients) median (IQR)	6 mo	34.5 (29–48)	36 (29–73)	.795	34.5 (29–48)	36 (29–73)	.829
Pain (no/mild/moderate/severe, n)	7 d	26/61/0/0	24/61/1/0	.657	26/56/0/0	24/56/1/0	.655
	30 d	70/17/0/0	71/14/0/0	.602	66/16/0/0	67/13/0/0	.589
	3 mo	74/5/0/0	74/6/0/0	.772	70/5/0/0	69/6/0/0	.755
	6 mo	75/5/0/0	76/4/0/0	.732	75/5/0/0	75/4/0/0	.747
Doctors' satisfaction at last follow-up, n (%)	Satisfactory	75 (91.5)	76 (92.7)	>.99	75 (91.5)	75 (92.6)	.983
	Normal	5 (6.1)	3 (3.7)		5 (6.1)	3 (3.7)	
	Unsatisfactory	2 (2.4)	3 (3.7)		2 (2.4)	3 (3.7)	
Participants' satisfaction at last follow-up, n (%)	Satisfactory	75 (91.5)	75 (91.5)	>.99	75 (91.5)	74 (92.5)	.870
	Normal	5 (6.1)	5 (6.1)		5 (6.1)	4 (5.0)	
	Unsatisfactory	2 (2.4)	2 (2.4)		2 (2.4)	2 (2.5)	

FAS = full analysis set, PPS = per-protocol set.

4. Discussion

Our study aimed to verify the efficacy and safety of the VIDASIS anal fistula plug manufactured by Biosis Healing. The Biosis porcine SIS can be widely used for tissue remodeling in humans due to its several advantages, such as easy absorption, trauma reduction, tissue regeneration, functional repair, complete degradation in vivo, and ability to maintain anal function and structure. Our clinical trial shows that not only is the anal fistula plug is safe and effective, it is also not inferior to existing SIS fistula plugs.

At present, surgery, mainly syringotomy and fistulotomy, is the most effective treatment method for anal fistula[1–4]; however, the high rates of recurrence, sequelae, and complications limit the overall effectiveness of these procedures.[6] Using a plug made from VIDASIS can be used for the successful treatment of anal fistula and help overcome these limitations.[10,11] VIDASIS has good histocompatibility and low immunogenicity owing to its biocompatibility.[7–9] Despite the promise of this material, residual DNA and α-gal may cause complications in some patients.[14,15]

However, VIDASIS was developed by Biosis Healing considering these complications. A study showed that using the Biosis SIS to repair large defects in the supraspinatus tendon in rabbits achieved similar outcomes to those of autologous tissue repair.[12] To the best of our knowledge, our study is the first to use VIDASIS in humans and show that it is not inferior to existing commercial SIS currently being used to treat anal fistulas. The Biosis SIS has been shown to have high mechanical strength,[16,17] and although this property is relevant to tendon repair, it is not favorable when used in a fistula plug. However, the main advantage of this product resides in its low immunogenic response,[18] which is crucial for fistula repair. Since the operation cannot be performed aseptically, reducing the immune burden of the wound is conducive to healing.

In the present trial, the healing rate with VIDASIS was not inferior compared to that with the commercial SIS, and patients in both groups showed healing rates of >90% at 6 months. The healing rate with xenograft plugs is reported to be 14% to 93% compared to 16% to 73% with synthetic plugs.[19–23] However, treatment efficacy may widely vary according to the complexity of the fistula (number of internal and external orifices), fistula location, and presence of bowel conditions. The patients enrolled in this trial had simple low anal fistula, and the results should be confirmed in patients with complicated diseases. Performing the LIFT-plug surgery in patients with complex anal fistula is regarded as being much more demanding to surgeons.[24,25]

The rate of adverse events and complications with the Biosis SIS was not remarkably different than that with the commercial SIS. This is supported by the overall favorable safety profile of SIS as a plug for anal fistula repair.[19–23]

Despite the promise of the trial, our study has some limitations. We used only 1 comparator SIS, and it remains unknown whether different SIS could achieve better outcomes. We did not assess inflammatory and immune response biomarkers; therefore, safety of the procedure cannot be completely ascertained. No patient developed fever after surgery, but subclinical inflammatory and immune changes were observed. Additional studies are necessary to examine the advantages of this novel SIS plug in humans. Furthermore, our study did not explore how body mass index and characteristics of the fistula affect treatment outcomes. Future studies should analyze the correlation between these factors to obtain robust results. As mentioned earlier, the LIFT-plug surgery is suitable in patients with simple anal fistula and those with a more complicated disease may not benefit from it as the sole treatment. The results of our study are short-term follow-up results and further studies should involve longer follow-up periods to thoroughly evaluate the efficacy of the treatment.

5. Conclusion

In summary, the anal fistula plug using the Biosis SIS is not inferior to the commercially available plug, as observed by the healing rate at 6 months. In addition, no remarkable differences were observed in the recurrence rate, copracrasia, healing time, pain, doctors' satisfaction rate, patients' satisfaction rate, and convenience of using the anal fistula plug. Furthermore, the safety endpoints, including postoperative vital signs, postoperative adverse responses, adverse events, and serious adverse events, were not remarkably different between the 2 groups. The findings of our study strongly suggest that the anal fistula plug produced by Biosis Healing is safe and effective for use in clinical practice.

Table 4

Adverse events (SS).

Adverse event	Time point	Experimental group, n = 87	Control group, n = 88	P
Fever, n (%)	1 d	0	0	–
Local infection, n (%)	7 d	0	0	–
	30 d	11 (12.6)	8 (9.1)	.450
	3 mo	11 (12.6)	7 (8.0)	.307
	6 mo	9 (10.3)	5 (5.7)	.256
Allergy, n (%)	All time points	0 (0)	0 (0)	–
Abscess, n (%)	7 d	0 (0)	0 (0)	–
	30 d	1 (1.2)	0 (0)	.497
	3 mo	1 (1.2)	1 (1.1)	1.000
	6 mo	0 (0)	2 (2.3)	.497
Acute or chronic inflammation, n (%)	7 d	0 (0)	0 (0)	–
	30 d	0 (0)	1 (1.1)	1.000
	3 mo	2 (2.3)	3 (3.4)	1.000
	6 mo	1 (1.2)	2 (2.3)	1.000
Others, n (%)	7 d	1 (1.2)	0 (0)	.497
	30 d	1 (1.2)	5 (5.7)	.211
	3 mo	1 (1.2)	10 (11.4)	.005
	6 mo	3 (3.5)	5 (5.7)	.720

SS = safety set.

Author contributions

Conceptualization: ZhaoWen Chen.
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Investigation: Rong Zhao, Yi Zheng.
Project administration: ZhenJun Wang.
Writing – original draft: Rong Zhao, Yi Zheng, ZhaoWen Chen, ZhenJun Wang.
Writing – review & editing: Rong Zhao, Yi Zheng, ZhaoWen Chen, ZhenJun Wang.

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